United States Senate

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Dockets Management Branch (HFA-305)
U.S. Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Docket No. 98N-0222, Dissemination of Information on Unapproved/New Uses for Marketed Drug, Biologics, and Devices

Dear Sir/Madam:

As the authors and principal legislative sponsors of Section 401 of S. 830, the Food and Drug Administration Modernization Act of 1997 (FDAMA), we are writing to express our strong concerns regarding the Food and Drug Administration's (FDA's) proposed rule "Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices," published in the Federal Register on June 8, 1998. Despite the fact that section 401 was the subject of extensive and exhaustive negotiations, FDA's proposed regulations appear to be at odds with the intent of the provision by imposing conditions that will negate or severely limit dissemination of valuable health information that was explicitly sanctioned under the statute. As drafted, FDA's proposed regulations are inconsistent with Congressional intent for section 401.

In the preamble to the proposal, FDA requests that interested parties provide concrete suggestions to address various issues contained in the proposal. This letter responds to that request. In doing so, we hope to work with the agency in order to ensure that the final regulations are consistent with Congressional intent.

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As clearly set forth in the legislative history, the intent of section 401 is to ensure that health care practitioners can obtain important scientific information about uses that are not included in the approved labeling of drugs, biologics and devices. As the Conference Report on FDAMA sets forth with regard to section 401:

> The Conference agreement's inclusion of this section is intended to provide that health care practitioners can obtain important scientific information about uses that are not included in the approved labeling of drugs, biological products and devices. The conferees also wish to encourage that these new uses be included on the product label.

H.R. Rep. 105-399 at 99 (1997).

The following statements from hearings on this issue further support that position:

> For me, the subject of today's hearing is very clear: Should the Federal Government stand as a roadblock in the free flow of responsible information to physicians about treatments which could mean the difference between life and death for many people with cancer and other diseases? I believe the questions should be answered with a resounding "No."

More Information for Better Patient Care: Hearing of the Senate Committee on Labor and Human Resources, 104th Cong. 2 (1996) (Statement of Senator Mack).

> A key question before us today is why the manufacturer of a potentially valuable product is forbidden to share that information with medical providers, people in the medical profession. No one is talking about allowing them to market those off-label uses or to advertise these uses, but what we are talking about is the facilitation of information flow within this controlled framework of the medical community.

More Information for Better Patient Care: Hearing of the Senate Committee on Labor and Human Resources, 104th Cong. 6 (1996) (Statement of Senator Frist).

As these statements indicate, in devising a program for dissemination of off-label information, in addition to facilitating the dissemination of medical information, Congress also sought to encourage, where appropriate, inclusion of such new uses on the product labels. Thus, section 401 of FDAMA strikes a careful balance between providing access to peer reviewed journals and reference publications (such as textbooks) that describe studies on "off-label" uses of approved products, and ensuring that research is undertaken to get such new uses on product labels. It is clear that the purpose of section 401 was limited to mandating greater dissemination of scientific information; the section does not authorize increased product promotion.

The system that Congress envisioned, and which was the subject of exhaustive consultation between FDA and Congressional staff, was one which would incorporate scientific and medical journals' existing criteria for scientifically sound articles. We did not intend for FDA to redefine the criteria by which journals that meet the statutory requirements for dissemination judge the soundness of such articles.

Through its proposed regulations, FDA is attempting: (1) to severely limit the types of information about clinical investigations that may be disseminated substantially beyond what we intended; (2) to circumscribe the statutory exemptions from the requirement to file a supplemental application; and (3) to devise an administrative process that frustrates Congressional intent that decisions be reached within sixty days on a company's request to disseminate the information.

The public policy underlying section 401 was the subject of extensive negotiations between FDA representatives and Congressional staff and was debated at length by the Congress. We included so much detail in this section in order to ensure that it maintained the balance that is critical to the success of this provision. The proposed regulations go beyond Congressional intent. We cite several prime examples of this below.

I. In Contradiction of the Statute, FDA's Proposed Regulations Dramatically Limit the Types of Clinical Investigations to Which Scientific Articles Intended for Dissemination May Pertain

The law authorizes dissemination of information on a new use of an approved product if the information is in the form of an unabridged:

> reprint or copy of an article, peer-reviewed by experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug or device involved, which was published in a scientific or medical journal . . . which is about a clinical investigation with respect to the drug or device, and which would be considered to be scientifically sound by such experts.

21 U.S.C. § 360aaa-1(a)(1). The statute also defines the term "scientific or medical journal." Indeed, Congress intentionally defined the term "scientific or medical journal" in the statute in order to avoid FDA defining the term or further limiting the information that could be disseminated. The statute defines a "scientific or medical journal" as

> a scientific or medical publication (A) that is published by an organization (i) that has an editorial board; (ii) that utilizes experts, who have demonstrated expertise in the subject of an article under review by the organization and who are independent of the organization, to review and objectively select, reject, or provide comments about proposed articles; and (iii) that has a publicly stated policy, to which the organization adheres, of full disclosures of any conflict of interest or biases for all authors or contributors involved with the journal or organization; (B) whose articles are peer-reviewed and published in accordance with the regular peer-review procedures of the organization; (C) that is generally recognized to be of national scope and reputation; (D) that is indexed in the Index Medicus of the National Library of Medicine of the National Institutes of Health; and (E) that is not in the form of a special supplement that has been funded in whole or in part by one or more manufacturers.

Thus, Congress set forth two criteria that an article must meet in order to be disseminated: (1) it must be about a clinical investigation and (2) it must be published in a scientific or medical journal as defined in the statute.

Despite the clear language of the statute, FDA has proposed regulations that would severely restrict manufacturers' ability to disseminate scientifically important articles. This is done by restricting dissemination to articles describing a narrow range of clinical trials and by requiring that the articles include more information about the trials than normally is contained in many peer-reviewed journal articles. For example, the statute identifies as an article that may be disseminated one ". . . which is about a clinical investigation with respect to the drug or device. . . ." 21 U.S.C. § 360aaa-1(a)(1). It explicitly contemplates that if such an article is published in a peer-reviewed journal and complies with the other criteria of the law it may be disseminated. Despite the clarity of the statute, FDA severely limits the types of articles that may be disseminated by defining "clinical investigation" as an investigation in humans that is prospectively planned to test a specific clinical hypothesis. Proposed 21 C.F.R. § 99.3(b). Such limitation usurps the role of the peer-reviewers of the scientific or medical journal and was not the intent of Congress.

FDA's proposed regulation also provides that:

> The determination of whether a clinical investigation is considered to be "scientifically sound" will rest on whether the design, conduct, data, and analysis of the investigation described or discussed in a reprint or copy of an article or in a reference publication reasonably support the conclusions reached by the authors.

Proposed 21 C.F.R. § 99.101(b)(1).

In the preamble to this proposed rule, FDA sets forth eight criteria for a "scientifically sound" clinical investigation. 63 Fed. Reg. at 31146-47. Those eight criteria, if applied by FDA, would place inappropriate limitations on the types of journal articles that may be disseminated. By defining what constitutes a scientifically sound clinical investigation, FDA, in essence, is defining for each and every peer-reviewed journal the criteria their experts should use to evaluate and publish articles. Further, the proposed regulations would allow FDA to substitute its judgment as to the scientific soundness of clinical investigations for the judgment of the peer reviewers as contemplated by the statute. It was not our intent to assign to the agency the role of independent reviewer of peer-reviewed scientific literature.

The discussions never focused on the need for the agency to define "clinical investigation;" rather, they focused on standards for qualified medical journals, which were incorporated into the statute. Thus, to the extent FDA's proposed regulations and accompanying preamble language impose specific requirements as to the type of investigations that must be described in peer-reviewed journals in order to be eligible for dissemination under section 401, the agency is circumventing Congress' decision to rely on the judgment of independent medical experts employed as part of the peer-review process of appropriate scientific or medical journals.

In sum, Congress determined that a copy of an article "about a clinical investigation" published in a scientific or medical journal was acceptable for dissemination, consistent with compliance with the other provisions of section 401. Accordingly, if an article about a clinical investigation published in a scientific or medical journal also met the requirements of the statute with regard to submissions to FDA regarding the conduct of clinical investigations or exemptions therefrom, and compliance with labeling requirements, including required disclosures and other information required by FDA, under the statute that article is acceptable for dissemination. Congress did not intend that FDA become the arbiter of what the publication criteria should be for every peer-reviewed journal. The eight criteria prescribed by FDA that an article must meet in order to be eligible for dissemination have no place in the implementation of the statute and should be deleted, as should FDA's definition of "scientifically sound." As long as the article and the manufacturer otherwise comply with the law, the regulation and accompanying preamble should be revised to make clear that the two statutory criteria, described above, are the only bases upon which an article may be disseminated.

II. FDA's Proposed Regulations Effectively Prohibit the Dissemination of Reference Publications

The agency also fails to consider Congressional intent with regard to reference publications. The law requires FDA to permit the distribution of reference publications, including reference texts, that meet the requirements of the statute. 21 U.S.C. § 360aaa-1(b). Like scientific or medical articles, truthful, nonmisleading reference texts are eligible for dissemination under the statute if they meet two criteria. First, they must include information about a clinical trial. Second, they must meet the statutory definition of a reference publication. A reference publication is carefully defined as a publication which: (1) has not been written, edited, excerpted, or published for or at the request of the manufacturer; (2) has not been edited or significantly influenced by the manufacturer; (3) has not been solely distributed through such a manufacturer; and (4) does not focus on any particular drug or device of the disseminating manufacturer. Id.

The agency fails to recognize the intent of Congress by proposing regulations that include a definition of "clinical investigation" that, by the agency's own admission, few, if any, reference texts can meet, thereby effectively prohibiting the distribution of reference publications.

FDA's discussion of the issue in the preamble implies that it is Congress' statute, not the agency's regulations, that effectively prohibit the dissemination of reference texts. FDA states that "[b]ecause the statute requires the information being disseminated to be about a clinical investigation, it seems unlikely that many reference publications will meet the requirements for dissemination under this provision." 63 Fed. Reg. at 31146. The statute is clear: FDA must allow the dissemination of reference texts that meet the requirements of the statute. It is the agency's proposed restrictions on what constitutes a "clinical investigation" that would prevent dissemination of reference materials.

FDA should revise the regulation to track the statute. As with articles in scientific or medical journals discussed above, FDA should revise the regulations to make clear that the statutory criteria control and should eliminate the additional criteria on clinical investigations discussed above. Moreover, if the agency fails to issue regulations that permit the dissemination of reference texts, the law makes it clear that section 401 will become effective November 21, 1998. 21 U.S.C. § 360aaa-6(d).

III. FDA Proposes to Unnecessarily Limit the Exemptions From Filing a Supplement

Congress balanced the dissemination of appropriate off-label information with a system that ensures that new uses described in such articles are properly studied and become approved. Congress did, however, recognize that there were several circumstances where it would be unnecessary or unwise to force a company to seek approval of these new uses. Therefore, Congress established two bases on which a company may be exempted from the statutory obligation to seek supplemental approval: (1) where it would be economically prohibitive for the manufacturer to incur the costs necessary for such a submission, taking into account the lack of any exclusive marketing rights and the size of the population expected to benefit from approval of the supplemental application; or (2) where it would be unethical to conduct the studies necessary for the supplemental application, taking into account whether the new use is the standard of medical care. 21 U.S.C. § 360aaa-3(d).

A. FDA's Criteria for Economically Prohibitive Supplements is Inconsistent with FDAMA

FDAMA authorizes FDA to waive the requirement for submission of a supplemental application on an off-label use upon a determination that it would be "economically prohibitive" to conduct the studies necessary to support the supplement. The criteria set forth in FDA's proposed regulations and accompanying preamble language for meeting this exemption are far more exacting than those contained in the statute. For example, FDA has proposed that to qualify for such exemption the manufacturer must demonstrate that the cost of studies needed to support the submission of a supplemental application will exceed the total revenue from *all sales* of the product (minus expenses) -- not just sales for the off-label use. Proposed 21 C.F.R. § 99.205(b)(1)(ii).

That was not our intent. Requiring that estimates of economic benefit to the manufacturer be equal to the prevalence of all diseases or conditions that the drug will be used to treat is at odds with the intent of the provision -- which was to authorize a waiver based on the economics of the *new use*.

The intent of the "economically prohibitive" exemption is demonstrated by examination of the statutory provisions themselves. The two statutory considerations that the Secretary "shall consider" in determining whether studies would be economically prohibitive are (a) the lack of exclusive marketing rights *with respect to the new use* and (b) the size of the population expected to benefit *from approval of the supplemental application.* 21 U.S.C. § 360aaa-4(d)(2)(A) (emphasis added).

B. FDA's Criteria for Exemption from Supplement Requirement Based on Ethical Issues is Inconsistent with FDAMA

FDA did not adhere to Congressional intent with respect to the second exemption from the requirement that the manufacturer file a supplemental application. Congress provided that a manufacturer should not be required to file a supplement where it would be unethical to do so. When a patient would be denied access to a therapy known or believed to be effective or where the patient would be denied the standard of medical care by taking part in a clinical trial, the manufacturer should not be required to conduct such trials in support of a supplemental application. Instead of adhering to Congressional intent, however, the FDA indicates that exemptions should be granted only "rarely".

In setting forth the criteria for when it would be "unethical to conduct studies necessary for the supplemental application", the statute states:

> In making such determination the Secretary *shall* consider (in addition to any other considerations the Secretary finds appropriate) whether the new use involved is the standard of medical care for a health condition.

21 U.S.C. § 360aaa-3(d)(2)(B). The Conference Report expounds on this notion:

> In making the determination of whether to grant an exemption pursuant to subsection (d)(2), the Secretary may consider, among other factors, whether: the new use meets the requirements of section 186(t)(2)(B) of the Social Security Act; a medical specialty society that is represented in or recognized by the Council of Medical Specialty Societies (or is a subspecialty of such society) or is recognized by the American Osteopathic Association, has found that the new use is consistent with sound medical practice; the new use is described in a recommendation or medical practice guideline of a Federal health agency, including the National Institutes of Health, the Agency for Health Care Policy Research, and the Centers for Disease Control and Prevention of the Department of Health and Human Services; the new use is described in one of three compendia: The U.S. Pharmacopoeia-Drug Information, the American Medical Association Drug Evaluation, or the American Hospital Association Formulary Service Drug Information; the new use involves a combination of products of more than one sponsor of a new drug application, a biological license application, a device premarket notification, or a device premarket approval application; or the patent status of the product.

H.R. Rep. 105-399 at 100.

FDA's proposed regulations set forth at 21 C.F.R. § 99.205(b)(2)(ii) would limit application of this exemption to only those situations when "withholding the drug in the course of conducting a controlled clinical study would *pose an unreasonable risk of harm* to human subjects." 63 Fed. Reg. at 31149 (emphasis added). FDA goes on to say that an unreasonable risk of harm ordinarily would arise only in situations in which the intended use of the drug appears to affect "mortality or irreversible morbidity". Id. To limit this exemption in the manner proposed is inconsistent with the statutory language that the Secretary consider whether the new use is the standard of care.[1]

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[1] The proposed regulation states that, "the manufacturer may provide evidence showing that the new use is broadly accepted as current standard medical treatment or therapy. The manufacturer shall also address the possibility of conducting studies in different populations or of modified design (e.g., adding the new therapy to existing treatments or using an alternative dose if monotherapy studies could not be accepted)." Proposed 21 C.F.R. § 99.205(b)(2)(ii).

Proposed 21 C.F.R. § 99.205(b)(2)(ii) should be revised in several ways in order to reflect Congressional intent. First, FDA should delete from the final regulation the limitation that only those studies in which the intended use of the drug appears to affect mortality or morbidity may be considered unethical. Second, FDA should include in the final regulation the language from the Conference Report quoted above which identifies when a new use may be considered a standard of medical care. Importantly, the regulation also should make clear that if a new use constitutes current standard medical care, it shall be considered unethical to require a study on such use and, thus, an exemption shall be granted.

IV. FDA's Proposed Regulations Attempt to Undermine the Statutory Requirement That FDA Respond to Submissions Within Sixty Days

The statute provides that when a manufacturer files a submission with FDA seeking to disseminate information, FDA must determine whether or not the submission meets the statutory criteria within sixty days. 21 U.S.C. §§ 360aaa(b), 360aaa-3(d)(3). It is irrelevant to Congress how the agency breaks down its review time in the intervening sixty days, but at the end of sixty days, FDA must determine whether complete submissions may be disseminated.

1. However, FDA's regulations propose that within sixty days of receiving a submission, the agency may determine whether it is approved, denied or the agency needs more information. Proposed 21 C.F.R. § 99.301(a). While it is appropriate for the agency to determine that it can only make such determinations on complete submissions, the agency fails to provide any time frames for obtaining additional information and responding to the manufacturer. As a result, the agency could request additional information on day 59, receive such information promptly, and then not respond to the submission for an undefined period of time. Any regulations promulgated by the agency should set specific time frames establishing how long the agency has to respond to a submission of additional information within the Congressionally-mandated sixty day period.

We also are concerned that proposed 21 C.F.R. § 99.205(d) states that the sixty day period begins when FDA receives a "complete submission" without further discussion of how long FDA may take to determine whether a submission is complete. The regulation should be revised to reflect our intent that any judgment as to completeness, as well as the decision to allow or disallow dissemination, should occur within sixty days. In an analogous situation, in its Prescription Drug User Fee Performance and Management Goals FDA sets 6 and 12 month time frames for approving applications or supplements thereto. Within those time frames, FDA makes judgment as to whether the application is acceptable for filing. The same process should occur here within the sixty day time frame.

To allow FDA an indeterminate amount of time before the sixty day time frame begins is not what Congress intended. The regulations should be explicit that the judgment as to the completeness of the submission shall occur within the overall sixty day time frame.

Lastly, the proposed regulations state that when a manufacturer submits a certification that it intends to conduct studies and submit a supplement within 36 months, the protocols must be submitted pursuant to an IND. Proposed 21 C.F.R. § 99.201(a)(ii)(4). Then, according to the preamble, "[t]he protocols will be reviewed as an original IND or IDE or an amendment to an existing IND or IDE." 63 Fed. Reg. at 31148. Under both the IND regulations, 21 C.F.R. part 312, and the IDE regulations, 21 C.F.R. part 812, FDA has thirty days to object to the initiation of the protocol. Under this proposed regulation, FDA has sixty days from the receipt of a complete submission to decide whether to allow the dissemination of the information. Proposed 21 C.F.R. § 99.201(d). It was not the intent of Congress that the sixty day time frame for a decision regarding dissemination be delayed as a result on ongoing IND negotiations. Therefore, the regulation should be clarified to state that nothing in this regulation is intended to lengthen the thirty day review period under the IND and IDE regulations cited above.

V. Conclusion

As drafted, FDA's proposed dissemination regulation does not reflect Congressional intent. We accept, in good faith, FDA's request that interested parties offer concrete changes to the proposal as published. We, in good faith, have responded to that offer with a number of concrete revisions to the regulation. While it is not our intention to advise FDA as to the precise approach its implementing regulations for section 401 of FDAMA should take, we are concerned with many aspects of the proposed regulations.

The purpose of Section 401 was to ensure the free-flow of objective scientific information to health care practitioners about new uses of FDA-approved products under specific circumstances. As drafted, the FDA regulations frustrate the objective of this provision. In addition, this is a time-limited program scheduled to sunset in 2006, or seven years after implementation. The provision also includes a requirement that a study be conducted to examine the scientific issues raised. Therefore, to assure a thorough examination of the issues raised by the enactment of these provisions, we believe it is important that Congressional intent be followed.

We strongly urge the agency to revisit the issues we have raised and to ensure that its final regulations are consistent with the statute and legislative history of this provision.

Sincerely,

Connie Mack
United States Senate

Bill Frist
United States Senate

James M. Jeffords
United States Senate

Christopher J. Dodd
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cc: Michael A. Friedman, M.D.
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